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Low degree of substitution of hydroxy propyl cellulose - by reacting cellulose with an alcohol, water and glucose.
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Abstract (Basic): JP 6100601 A
Hydroxypropyl cellulose with a low degree of substn. and high solubility in aq. alkali soln. has a degree of hydroxy propyl substn.
(0.2-0.9) and viscosity of 2 wt. % in aq. 8 wt. % sodium hydroxide soln. at least 1000 centipoise.
Prepn. is carried out by making cellulose react with 10-20 wt. % times of a mixed medium consisting of 85-92 wt. % of tert-butyl alcohol, a residual amt. of water and 0.8-1.5 mol. anhydrous gluclose
unit of cellulose of alkali. Alkali cellulose forms and reacts with 1.1-5.0 mol. anhydrous glucose unit of the cellulose of propylene oxide
at 50-70 deg.C for 2--5 hrs.
USE/ADVANTAGE - The low degree of substn. hydroxy-propyl cellulose
can be used for coating tablets, because it has good solubility in alkali solvent in forming coating films and shows good degradation in
tablet form.
In an example, the cellulose is wood pulp, linter etc. used after
breaking by hammer mill etc.
Dwg.0/0
Title Terms: LOW; DEGREE; SUBSTITUTE; HYDROXY; PROPYL; CELLULOSE; REACT; CELLULOSE; ALCOHOL; WATER; GLUCOSE
Derwent Class: A11; A96; B07
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(54) [Title of the invention]

Slightly substituted hydroxypropylcellulose having the high solubility in an aqueous alkali solution and a process for preparing the same

[Claims]

[Claim 1] Slightly substituted hydroxypropylcellulose having the high solubility in an aqueous alkali solution, which has a hydroxypropyl substitution degree of a range of 0.2 to 0.9, and which has the viscosity of 1000 centipoise or larger at 25°C of a solution having the concentration of 2% by weight in a 8% by weight aqueous sodium hydroxide solution.

[Claim 2] A process for preparing slightly substituted hydroxypropylcellulose as defined in claim 1, which comprises reacting 10 to 20-fold weight relative to cellulose weight of a mixed medium comprising 85 to 92% by weight of tert-butyl alcohol and the balance of water and 0.8 to 1.5 mole per anhydrous glucose unit of cellulose of an alkali with cellulose to obtain alkalicellulose, which is reacted with 1.1 to 5.0 mole per anhydrous glucose unit of cellulose of propylene oxide at 50 to 70°C for 2 to 5 hours.

[Detailed description of the invention]

[0001]

[Industrial field of utilization] The present invention relates to slightly substituted hydroxypropylcellulose which is

extremely dissolved in an aqueous alkali solution, in which that aqueous solution has the excellent transparency and can easily form a film or a coating film, and a process for preparing the same.

[0002]

[Prior art and problems thereof] There are a huge number of studies on cellulose ether in the past. Regarding a process for preparing, in particular, hydroxyalkylcellulose, a huge number of proposal were made because derivatives thereof are extremely useful in a variety of uses.

[0003] Regarding a process for preparing hydroxypropylcellulose (hereinafter abbreviated as HPC), many proposals have made. Generally, cellulose ether is used because it is water-soluble and produces the effects of increasing the effects of its aqueous solution and the effects as a protective colloid. This HPC is not only water-soluble but also soluble in an organic solvent, and is excellent in film forming and, thus, has been used for coating a tablet, and so on. However, previous HPC must have a hydroxpropyl substitution degree of 3 or more, preferably 3.5 or more in order to make it soluble in an organic solvent. Therefore, proposals regarding a process for preparing it were made naturally only on HPC having such the substitution degree.

[0004] However, recently, it has been found that HPC insoluble in an organic solvent to water is suitable for coating a tablet

and is excellent in the disintegrating property of a tablet and, thus, proposals of utilizing slightly substituted HPC in the use have been made. However, a process for preparing slightly substituted HPC is described only in JP-B 57-59857. The content thereof relates to HPC having a substitution degree of 0.05 to 0.40, in which a water-soluble part at 20°C is 10% by weight or less, a part soluble in a 8% aqueous sodium hydroxide solution at 20°C is 90% by weight or more, and the viscosity at 20°C and at the concentration of 2% by weight of a 8% aqueous sodium hydroxide solution is 5 to 500 centipoise. In deed, slightly substituted HPC shown in this gazette is excellent in the disintegrating property of a tablet. However, since it is worse in the solubility in a solvent at formation of a coating film, the great film strength can not be obtained and use of it alone produces no uniformity of a coating film and, thus, means such as use of it together with highly substituted HPC was taken.

[0005]

[Means to solve the invention] The present inventors extensively studied in order to solve these problems and, as a result, by adjusting the concentration of an alkali used as a reaction catalyst upon preparation of slightly substituted HPC and by using as a reaction solvent tert-butyl alcohol at a specified ratio relative to cellulose, slightly substituted HPC having the excellent solubility in an alkali solvent at formation of a coating film and having the better disintegrating

property of a table is obtained, which resulted in completion of the present invention.

[0006] That is, the present invention provides slightly substituted hydroxypropylcellulose having the high solubility in an aqueous alkali solution, which has a hydroxypropyl substitution degree of a range of 0.2 to 0.9, and which has the viscosity of 1000 centipoise or larger at 25°C of a solution having the concentration of 2% by weight in a 8% by weight aqueous sodium hydroxide solution, as well as a process for preparing slightly substituted hydroxypropylcellulose as defined in claim 1, which comprises reacting 10 to 20-fold weight relative to cellulose weight of a mixed medium comprising 85 to 92% by weight of tert-butyl alcohol and the balance of water and 0.8 to 1.5 mole per anhydrous glucose unit of cellulose of an alkali with cellulose to obtain alkalicellulose, which is reacted with 1.1 to 5.0 mole per anhydrous glucose unit of cellulose of propylene oxide at 50 to 70°C for 2 to 5 hours.

[0007] As cellulose used in the present invention, any celluloses such as a timber pulp and a linter which are usually used in a chemical reaction may be used. In addition, cellulose which has been crushed with a hammer mill or the like prior to a reaction is preferable.

[0008] In the present invention, first, cellulose is reacted with an alkali in a mixed medium of tert-butyl alcohol and water to obtain alkalicellulose (mercerization). It is preferable

that the composition of a mixed medium to be used is such that a ratio of tert-butyl alcohol relative to total of tert-butyl alcohol and water is in a range of 85 to 92%. This mixed medium is used at an amount of 10 to 20-fold weight relative to weight of cellulose.

[0009] As an alkali, various alkalis such as sodium hydroxide, potassium hydroxide and lithium hydroxide are used. From a viewpoint of industry, it is desirable that sodium hydroxide is used. The concentration of an alkali is extremely important in the present invention. In order to obtain slightly substituted HPC of the present invention, 0.8 mole or more of an alkali is necessary per anhydrous glucose unit of cellulose. In a desired range of 0.2 to 0.9 of a hydroxypropyl substitution degree, it is sufficient that an alkali is used at 0.5 mole or smaller per anhydrous glucose unit of cellulose used in a reaction. That is, when an amount or an alkali is 0.8 mole or smaller per anhydrous glucose unit of cellulose, the effects of the present invention can not been obtained. On the other hand, when the amount is 1.5 mole or more, the effects remain unchanged but a large amount of a salt is produced at a large amount at neutralization and, thus, washing is laborious and uneconomical. A preferable amount of an alkali to be used is 1.0 to 1.4 mole per anhydrous glucose unit of cellulose. Mercerization is desirably performed at 10 to 15°C for 1 to 4 hours.

[0010] Then, the thus obtained alkalicellulose is reacted with propylene oxide. propylene oxide used in the present invention is 1.1 to 5.0 mole per anhydrous glucose unit of cellulose. Since a reaction makes a hydroxypropyl substitution degree 0.2 to 0.9, it is necessary to perform a reaction at 50 to 75°C for 2 to 5 hours. When a reaction time is shorter than 2 hours, a sufficient substitution degree of slightly substituted HPC can not be obtained and the solubility in an aqueous alkali solution becomes worse.

[0011] After completion of a reaction, it is necessary to neutralize sodium hydroxide with an inorganic acid and wash the product with an aqueous acetone solution or water. Drying is sufficiently performed at 105°C for few hours.

[0012] The thus obtained slightly substituted HPC has a hydroxypropyl group of 0.2 to 0.9 mole per anhydrous glucose unit, and has the extremely better film forming ability, film strength and disintegrating property of a tablet. The aforementioned JP-B 57-59857 describes that HPC having the number of a hydroxypropyl group per glucose unit of 0.05 to 0.4 is better. There is a description that the reason is that, in the case of 0.05 or smaller, the solubility in an aqueous alkali solution becomes worse, on the other hand, in the case of 0.4 or greater, since the solubility in water is increased, the function as disintegrating agent is deteriorated. However, there was seen phenomenon that slightly substituted HPC

obtained by the present inventors has not the increased solubility in water even when a hydroxypropyl group substitution degree is 0.4 or more and, on the other hand, it is approximately completely dissolved in an aqueous alkali solution. It is considered that this has a relationship with distribution of a substituent caused by a process for preparation of the present invention. That is, it is presumed that since the concentration of an alkali is high in the process for preparation of the present invention, a hydroxy group at a 6-position of glucose is selectively reacted and, as a result, a difference in the solubility is manifested.

[0013]

[Examples] The present invention will be illustrated by way of Examples below but the present invention is not limited to these Examples.

[0014] Example 1

20 parts by weight of a linter which had been crushed with a cutting mill was placed in a separable flask, 268 parts by weight or t-butyl alcohol and 20 parts by weight of water were added thereto to obtain a slurry, an aqueous sodium hydroxide solution obtained by dissolving 1.2 mole per anhydrous glucose unit of sodium hydroxide in 12 parts by weight of water was added, and mercerization was performed for 1 hour while stirring. At this time, a ratio of t-butyl alcohol to a total of t-butyl alcohol and water was 89%. After mercerization, propylene oxide was

added at 5 moles per anhydrous glucose unit, and a reaction was performed at 75°C for 3 hours. After a reaction, the reaction is cooled, neutralized with nitric acid, desolated, washed with 400 parts by weight of a 70% by weight aqueous acetone solution four times. After washing, the product was dried at 105°C.

[0015] The nature of the thus obtained slightly substituted HPC is shown in Table 1. (1) hydroxypropyl substitution degree (MS), (2) viscosity of an aqueous solution and (3) transparency of an aqueous solution as a nature of slightly substituted HPC were measured as follows:

(1) Substitution degree: A hydroxypropyl group was oxidation-degraded using chromium trioxide, or a hydroxypropyl group was freed and iodinated using hydroiodic acid and these degradation products were measured quantitatively.

(2) Viscosity of an aqueous solution: a sample was dissolved in a 8% aqueous sodium hydroxide solution at the concentration of 2%, and the viscosity is measured using a B-type viscometer at 25°C. The viscosity of an aqueous solution is expressed merely as viscosity in table, hereinafter.

(3) Transparency of an aqueous solution: a good quality glass plate having a thickness of 2 mm was adhered to the bottom of a glass cylinder having a height of 350 mm, an inner diameter of 25 mm and a thickness of 2 mm, which was used as an external tube. A good quality glass plate having a thickness of 2 mm was adhered to the bottom a glass cylinder having a height of

300 mm, an inner diameter of 15 mm and a thickness of 2 mm, which was used as an inner tube. A test solution was placed in the external tube, which was placed on a white paper on which 15 parallel lines were drawn at a black color at intervals of 1 mm. When an inner tube was moved upwardly and downwardly and is seen through from its upper part, a height to a lower end of the inner tube when lines can not be discriminated is measured. This procedures were repeated three times and an average is expressed in mm unit. In Table, transparency of an aqueous solution is expressed merely as transparency.

[0016] Example 2 and Comparative of Example 1

According to the same manner as that of Example 1 except that a hydroxypropylation time was as shown in Table 1, slightly substituted HPC was prepared. The nature of the resulting slightly substituted HPC is shown in Table 1 together with the results of Example 1. In Comparative Example 1 in which hydroxypropylation was performed for 1 hour, a sufficient substitution degree was not obtained, and transparency of an aqueous alkali solution was very worse.

[0017]

[Table 1]

	Reaction time* (hr.)	Amount of propylene oxide to be placed (mol/anhydrous glucose unit)	Substitution degree	Viscosity of 2% aqueous solution	Transparency (mm)
Example 1	3	5	0.62	2680 cP	350
Example 2	2	5	0.31	3360 cP	350
Comparative Example 1	1	5	0.16	1380 cP	95

* Reaction time: time of a hydroxypropylation reaction

[0018] Examples 3 to 5 and Comparative Example 2

According to the same manner as that of Example 1 except that, after a hydroxypropylation reaction was performed at 60°C for 1 hour, a temperature was raised to 70°C, and a reaction time was changed as shown in the following Table 2, preparation of slightly substituted HPC was performed. The nature of resulting slightly substituted HPC is shown in Table 2. As in Comparative Example 2, only a reaction at 60°C for 1 hour did not afford a sufficient substitution degree and the product was hardly dissolved in an aqueous alkali solution.

[0019]

[Table 2]

	70°C reaction time	Amount of propylene oxide to be placed (mol/anhydrous glucose unit)	Substitution degree	Viscosity of 2% aqueous solution	Transparency (mm)
Comparative Example 2	0 hour	5	0.06	70 cP	27
Example 3	1 hour	5	0.23	2180 cP	100
Example 4	2 hours	5	0.47	2900 cP	192
Example 5	3 hours	5	0.72	5000 cP	300

[0020] Examples 6 to 8 and Comparative Example 3

According to the same manner as that of Example 1 except that an amount of propylene oxide to be placed was as shown in the following Table 3, a reaction was performed at 60°C for 1 hour and then at 70°C for 2 hours, preparation of slightly substituted HPC was performed. The nature of the resulting slightly substituted HPC is shown in Table 3. As in Comparative Example 3, when a reaction is performed at an amount of propylene oxide to be placed of 1 mole per anhydrous glucose unit, a sufficient substitution degree was not obtained and the product was hardly dissolved in an aqueous alkali solution.

[0021]

[Table 3]

	Reaction temperature and time* (°C × hr.)	Amount of propylene oxide to be placed (mol/anhydrous glucose unit)	Substitution degree	Viscosity of 2% aqueous solution	Transparency (mm)
Comparative Example 3	60°C × 1 hr 70°C × 2 hr	1.0	0.08	80	23
Example 6	60°C × 1 hr 70°C × 2 hr	1.5	0.21	1200	150
Example 7	60°C × 1 hr 70°C × 2 hr	3.0	0.31	1390	160
Example 8	60°C × 1 hr 70°C × 2 hr	5.0	0.47	2900	190

* Reaction temperature and hour; temperature and time of a hydroxypropylation reaction

[0022] Comparative Example 4

According to the same manner as that of Example 1 except that an amount of sodium hydroxide to be placed was 0.75 mole per

anhydrous glucose unit, preparation of slightly substituted HPC was performed. Since a substitution degree of the resulting slightly substituted HPC was not sufficient as being 0.14, the product was hardly dissolved in an aqueous alkali solution.

[0023] Comparative Example 5

According to the same manner as that of Example 1 except that an amount of sodium hydroxide to be placed was 1.8 mole per anhydrous glucose unit, preparation of slightly substituted HPC was performed. Since a substitution degree of resulting slightly substituted HPC was insufficient as being 0.18, the product was hardly dissolved in an aqueous alkali solution.

[0024] Comparative Example 6

According to the same manner of as that of Example 1 except that a ratio of tert-butyl alcohol relative to a total of tert-butyl alcohol and water was 80%, preparation of slightly substituted HPC was performed. Since a substitution degree of the resulting slightly substituted HPC was insufficient as being 0.07, the product was hardly dissolved in an aqueous alkali solution.

[0025] Comparative Example 7

According to the same manner as that of Example 1 except that only tert-butyl alcohol was used as a reaction medium and water was not added at all, preparation of slightly substituted HPC was performed. Since a substitution degree of the resulting slightly substituted HPC was insufficient as being 0.04, the product was hardly dissolved in an aqueous alkali solution.

[0026] Examples 9 and 10

The solubilities of the present slightly substituted HPCs obtained in Examples 3 and 4 were compared. The results are shown in Table 4.

[0027]

[Table 4]

		HPC	Substitution degree	Water-soluble fraction
Example	9	Example 3	0.23	4.4%
	10	Example 4	0.47	6.1%

[0028] Comparative Example 8

Regarding commercially available slightly substituted HPC (L-HPC, grade LH21 manufactured by Shinetsu kagaku koughou (K.K.)), according to the same manner as that of Example 1, a substitution degree, viscosity of an aqueous solution, transparency of an aqueous solution and solubility in a water were measured. The results thereof are shown in Table 5 together with the results of slightly substituted HPCs of Examples 3 and 4.

[0029]

[Table 5]

	Substitution degree	Viscosity of a 2% aqueous solution	Transparency (mm)	Water-soluble fraction
Comparative Example 8 (LH 21)	0.35	35 cP	38	2.0
Example 3	0.23	2180 cP	100	4.4
Example 4	0.47	2900 cP	192	6.1

[0030] From Table 5, it is seen that, slightly substituted HPC obtained by the present invention, even having a low substitution degree as compared with commercially available slightly subsbtituted HPC, has a water-soluble fraction having slightly higher substitution degree than commercially available slightly substituted HPC and having the very excellent solubility in an aqueous alkali solution.

[0031] Example 11 and Comparative Examples 9 and 10

Slightly substituted HPCs shown in the aforementioned Example 3、Comparative Example 2 and Comparative Example 8 were dissolved in a 8% aqueous sodium hydroxide solution to the concentration of 7%, respectively, allowed to stand to a temperature of 0°C, cast on a glass plate, which were coagulated in a 20% aqueous ammonium sulfate solution, a salt was removed by washing with water, and dried at 70°C to obtain films. A film thickness, appearance and transparency of the resulting films were evaluated. A thickness of a film was measured with a microgauge. In evaluation of appearance and transparency of films, ◎ means better, △ means normal, and × means worse. The results are shown in Table 6.

[0032]

[Table 6]

	HPC	Substitution degree	Viscosity of a 2% aqueous solution	Thickness (mm)	Appearance of a film	Transparency of a film
Example 11	Example 3	0.23	2180 cP	0.022	◎	◎, Colorless and transparent
Comparative Example 9	Comparative Example 2	0.06	70 cP	0.023	×	×, White clouding
Comparative Example 10	LH21	0.35	35 cP	0.023	△	×, Yellow clouding

[0033] From Table 6, it is seen that a film comprising slightly substituted HPC of the present invention is excellent in transparency and uniformity as compared with a film of Comparative Example.

[0034] Example 12 and Comparative Examples 11 and 12

Tablets were prepared using as a disintegrating agent slightly substituted HPCs shown in the aforementioned Example 3, Comparative Example 2 and Comparative Example 8, and a compressing test was performed. The composition of a tablet and preparation conditions are as follows:

(1) Composition of a tablet

Disintegrating agent (slightly substituted HPC)	3 parts by weight
Lactose	17 parts by weight
Avicel PH101	23 parts by weight
Talc	2 parts by weight
Aspirin	55 parts by weight
Total	100 parts by weight

(2) Preparation conditions

Compressing machine: manufactured by Kikusui seisakusyo, Cleanpresscollect 19

Molding conditions: tablet diameter 8 mmϕ, tablet thickness 2mm weight 250 mg

The physical properties of a tablet were measured by the following method. The results are shown in Table 7.

Hardness: Monsanto hardness tester was used.

Disintegrating property: the property was measured according to a test method of Japanese pharmacopoeia and water (22) ± 1°C was used as a test liquid.

[0035]

[Table 7]

	HPC	Substitution degree	Viscosity of a 2% aqueous solution	Hardness (kg)	Disintegrating property (sec)
Example 12	Example 3	0.23	2180 cP	14.0	57
Comparative Example 11	Comparative Example 2	0.06	70 cP	9.7	66
Comparative Example 12	LH21	0.35	35 cP	11.5	65

[0036] From Table 7, it is seen that a tablet of Example 12 has the excellent the disintegrating property and the hardness as compared with tablet of Comparative Example 11 and Comparative Example 12.

(57) [Abstract]

[Construction] Slightly substituted hydroxypropylcellulose having a hydroxypropyl substitution of a range of 0.2 to 0.9 and having the viscosity of 1000 centipoise or larger at 20°C and at the concentration of 2% by weight of a 8% by weight aqueous sodium hydroxide solution. This slightly substituted hydroxypropylcellulose is prepared by reacting a specified amount of a mixed medium comprising 85 to 92% by weight of tert-butyl alcohol and the balance of water and a specified amount of an alkali with cellulose to obtain alkalicellulose, which is reacted with a specified amount of propylene oxide under the specified conditions.

[Effects] The slightly substituted hydroxypropylcellulose has the high solubility in an aqueous solution and has the low solubility in water and, thus, it is effective for coating, in particular, tablets and maintains the disintegrating property of tablets.